Berson, Eliot 2006

Dr. Berson Eliot Oral History 2006

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Interview with Dr. Eliot Berson

Conducted by: Dr. Carl Kupfer
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Association for Research in Vision and Ophthalmology
ARVO

Dr. Kupfer: I am meeting with Dr. Eliot Berson in ARVO and I will be interviewing him for the history of the National Eye Institute (NEI). Eliot, thank you very much for agreeing to be interviewed for the history of the National Eye Institute. I suppose we ought to begin with which dates you were at the National Institute of Neurological Diseases and Blindness (NINDB) as a member of the Ophthalmology Branch.

Dr. Berson: Dr. Kupfer, thank you for giving me this opportunity to share some of my experiences in the Ophthalmology Branch of NINDB. It was a critical period in my education that has profoundly influenced my research direction. As you know I am the William F. Chatlos Professor of Ophthalmology at Harvard Medical School and Director of the Berman-Gund Laboratory for the Study of Retinal Degenerations at the Massachusetts Eye & Ear Infirmary. In July1966, I was appointed as a clinical associate in the Ophthalmology Branch by the late Dr. Ludwig von Sallmann following residency training at Washington University School of Medicine. I viewed this appointment as an opportunity to expand my research horizons and in the process serve patients with diseases that were at that time untreatable. When I arrived at NINDB, we were told on orientation day that there were four major projects, namely heredity retinal diseases, glaucoma, ocular tumors, and uveitis. At first, because my research experience at Harvard Medical School had been in infectious diseases, I thought that I would focus on uveitis, but I became convinced that hereditary retinal diseases posed the greatest challenge both with respect to understanding the causes and seeking means for treatment. The Ophthalmology Branch had pioneered the development of electroretinographic testing as an aid in assessing patients with hereditary retinal diseases. The electroretinogram or ERG is a measure of retinal function; responses are obtained in response to brief flashes of light with a specialized contact lens electrode placed on the topically anesthetized cornea, much as a an electrocardiogram is recorded from the heart. Dr. von Sallmann had assembled a group of scientists over a ten-year period to help perfect the methodology for recording ERGs. I was impressed with the reproducibility and sensitivity of these responses and therefore I volunteered to use the ERG as an aid in assessing patients with hereditary retinal diseases, in particular, retinitis pigmentosa. Dr. von Sallmann, in turn, introduced me to two senior scientists, Dr. Michaelangelo Fourtes and Dr. Peter Gouras who had expertise in the area of recording ERGs. The research effort on retinal disease was also enhanced by Dr. Arnaldo Lasansky who was working on retinal ultrastructure and by Dr. Paul O'Brien who was studying retinal biochemistry. I was also fortunate to be working with a very highly talented group of clinical associates who were interested in retinal diseases, specifically Dr. Daniel Albert, whose focus was retinal tumors; and Dr. Richard Smith, who was studying retinal pathology. Dr. Vernon Wong, the Associate Director, whose research area was uveitis, was interested in the consequences of inflammatory disease on retinal function. We also benefited from the expertise of visiting consultants, particularly Dr. Lorenz Zimmerman from the Armed Forces Institute of Pathology and Dr. A. Edward Maumenee from Johns Hopkins University. Therefore, from my perspective the Ophthalmology Branch provided an unusual, if not unique, environment, for the study of retinal degenerations.

Dr. Kupfer: Well, that seemed like an ideal situation for a young person coming out of a residency and then being able to focus on research. Presumably you then became part of Dr. Peter Gouras' laboratory.

Dr. Berson: Yes, Dr. Gouras offered guidance in recording ERGs from animals and provided me with a space to perform this research. In the laboratory, I could rearrange the recording equipment and see the consequences with respect to the ERG responses. Dr. von Sallmann encouraged this so that I would have firsthand knowledge of how to establish a system for recording ERGs. This was a critical part of the training.

Dr. Kupfer: Did Dr. von Sallmann play an active role in supervising the research or did he leave it up to you to handle?

Dr. Berson: From my view, he was a perfect mentor. He had enormous clinical experience going back to his days as a professor of ophthalmology at the University of Vienna and then as a research professor at Columbia University. Because of his reputation, patients came from all over the United States and even abroad for consultation. The clinic for hereditary retinal diseases met every Monday. He would examine every patient with me and then we would adjourn to a side room to discuss the details of the case. He felt it was better to have our conference about each patient first and then together speak with the patient. To me it was an honor to examine patients under his supervision. He shared with me not only his perspective but also what other ophthalmologists thought about these diseases over the past 50 years. He insisted that, as part of my education, I should go to the NIH library a half day each week and, with the aid of an interpreter of old German, review the atlases that contained drawings of retinal diseases made in the early part of the twentieth century before they had fundus photography. He encouraged me to select diseases that I had never seen firsthand and he, in turn, usually would recall a patient that he had examined with that condition over the past ten years at the NIH. He would authorize me to contact the patient and invite him or her for a clinical assessment including ERGs. The patients were very grateful that we had continued interest in their problems and I was very appreciative because I had the opportunity to see unusual cases in a supervised setting. Some of these patients became the subject of our publications. I examined several thousand patients with him from 1966-1968. I was interested in the hypothesis that light stress aggravated these diseases, and Dr. von Sallmann allowed me to admit three siblings to our inpatient floor to assess the short-term effects of light deprivation. We patched one eye of these patients for a week and tried to learn whether light deprivation modified retinal function. These patients were subsequently found by us in Boston to have a rhodopsin, Pro-23-His mutation, and although they did not show improved retinal function in the short-term, there is now some experimental evidence to support the idea that light protection might help these patients. In addition, as a part of the education process, we had a meeting, just like medical grand rounds, every Tuesday and one of the associates was responsible for presenting some cases to Dr. von Sallmann and the clinical staff; we had formal discussion about management of these conditions and what research should be done. Dr. von Sallmann read the papers that we wrote prior to publication and this contributed to my learning more about how to write a scientific paper. Dr. Peter Gouras was also participatory and very helpful in my education. During this period, we were the first to demonstrate that patients with the early stages of progressive forms of retinitis pigmentosa had ERG responses that were not only reduced in amplitude but also delayed in their peak implicit times (i.e., the time interval between stimulus onset and the major cornea-positive peak of the cone or rod response). These abnormal ERGs could be often detected years to a decade before the patient developed visual symptoms or fundus changes could be seen on a conventional ocular examination. The ERGs of those with progressive retinal disease had delayed implicit times that contrasted with those with self-limited or stationary retinal disease in which the amplitudes could be reduced but the implicit times were normal. This capacity to detect patients with early stages of progressive disease would subsequently prove to be critical in selecting appropriate patients for clinical treatment trials aimed at stabilizing or slowing retinitis pigmentosa. We were also interested in drug toxicities because toxic effects of some medications on the retina in some cases simulated the effects of hereditary retinal diseases. For example, chloroquine toxicity in an advanced stage can result in fundus changes that resemble retinitis pigmentosa. In the 1960's, the Ophthalmology Branch was quite instrumental in demonstrating that chloroquine (Aralen) was potentially retinotoxic. This was a significant finding because it led physicians to abandon chloroquine and to use hydroxychloroquine (Plaquenil), which appeared to be a potentially less toxic medication for the treatment of lupus erythematosus or rheumatoid arthritis. We assessed chloroquine not only clinically but also in a laboratory model and found that acute toxicity to the retina could be produced with a single intravitreal injection of chloroquine.

Dr. Kupfer: This sounds very, very positive in terms of the opportunity for a young person to develop research capabilities. And I suppose one might ask were there any limitations on what Dr. von Sallmann could do to help you. For instance, whether meetings that were being held to which it would have been good for you to be invited and participate, was there a travel budget that allowed the clinical associates to take advantage of this sort of thing?

Dr. Berson: We have to remember that the Ophthalmology Branch was not only involved in clinical and laboratory research, but the clinical associates in the Branch provided ophthalmic services to the rest of the NIH. To my recollection there were some 500 - 1,000 inpatients in the various institutes of NIH who sometimes had not only systemic diseases but also eye disease associated with their systemic conditions. We were expected to be on-call for their needs, and therefore given the small size of our staff, we went to research meetings only occasionally. I do remember that I attended one meeting of the Association for Research in Vision and Ophthalmology in my second year. Further, I did have to take my specialty board certification examinations to permit me to subsequently join the Harvard Medical School faculty. Dr. von Sallmann understood this requirement and therefore graciously gave me a three-day leave of absence to take this examination. Beyond these brief leaves, it was the general understanding that the clinical associates were on call for patients admitted to the clinical center at the NIH and we took this responsibility very seriously.

Dr. Kupfer: After Dr. Arnall Patz had demonstrated the effects of oxygen in producing retrolental fibroplasia in a small clinical trial, the Neurology section of the NINDB mounted a large collaborative trial that confirmed his observation. Did that study impact at all upon the Intramural group?

Dr. Berson: I don't recall that but I must say that was not my focus at that time. In reply to your earlier question about limitations in the Ophthalmology Branch, there was one limitation that remains vivid in my memory. It was the small size of the room for housing animals for research. When I was in the Ophthalmology Branch, I always felt that the animal room was not adequate for the number of physicians and scientists doing research. We were particularly interested in a nocturnal monkey called the "galago" that was thought to have a retinitis pigmentosa-like fundus picture, possibly due to the fact that this monkey was on display during the day at the Smithsonian Zoo and thereby might have suffered from excessive light exposure. Dr. von Sallmann shared with me an interest in learning about whether light exposure could aggravate the course of retinitis pigmentosa. Therefore, he agreed that we should obtain four of these galago monkeys and expose them to various amounts of light. But the biggest logistic problem was not obtaining the monkeys but convincing the attendant in the animal room that he should make space to study these monkeys. Despite the space constraints, the animal attendant finally agreed and the project was done; we found that ordinary light exposure did not produce retinal degeneration in these animals.

Dr. Kupfer: Was this space part of Neurology's Intramural space?

Dr. Berson: I believe it was a shared animal room and, in retrospect, I think more could have been done if we had more space for animals. On the other hand, we had an extraordinary space for clinical research on patients with ocular disease; specifically we had twenty beds in the NIH Clinical Center and we admitted patients with problems such as chronic uveitis to evaluate various medications to control inflammation. This required daily patient observation to follow the course of inflammation. We also admitted some patients with hereditary retinal degenerations and searched for biochemical abnormalities in these conditions. The space to study patients was not limited in contrast to the animal space.

Dr. Kupfer: With uveitis I recall this was a major activity—I forget how many thousands of patients had been seen with uveitis but I was under the impression

that there were defined protocols to study these patients.

Dr. Berson: You are quite correct with regard to uveitis. However, it was only after the evolution of the National Eye Institute and the rigorous implementation of clinical trial methodology, which I wish to be on record as giving you credit for establishing, that drugs and nutritional supplements were evaluated in a way that took into account appropriate controls, data monitoring, and modern statistical methodology. With respect to clinical trial methodology, I had to wait until I returned to Harvard Medical School to learn more about this methodology. While at Harvard, I learned this methodology in large part due to the programs implemented by the National Eye Institute. The scientific training and clinical exposure at the NINDB was for me a superb experience but the whole issue of statistical approaches in medicine, including determining sample sizes in which to conduct studies, etc., was not an integral part of the clinical eye research until the epidemiology unit was established in the National Eye Institute under your directorship. However, my training in visual function assessment with the ERG, which later would become the main outcome measure in our clinical trial of vitamin A for retinitis pigmentosa, was critical in our ability to conduct a phase III trial for patients with retinitis pigmentosa. This would not have been possible without my previous experience in the Ophthalmology Branch.

Dr. Kupfer: It's interesting you bring up the fact that there wasn't much being done in terms of bio-statistical analysis of data in patients with ocular disease and yet some of the greatest strides forward using bio-statistical analyses were made by NIH scientists. In fact in the early 1950s the Cancer Institute recruited a number of statisticians and Dr. Shannon was so excited by this that he actually pulled them out of the Cancer Institute and put them in his office to take care of the needs of everyone at the NIH.

Dr. Berson: Is that so? I didn't know that.

Dr. Kupfer: Yes. But apparently you had to ask for help.

Dr. Berson: In retrospect, we were studying individual families with retinal degenerations rather than large groups of patients at a later time, and therefore the research did not lend itself to extensive bio-statistical studies. Also looking back, we were so grateful for the opportunity we had and so occupied with the research at hand, we were not prone to talk, at least at my level, about activities we couldn't do or resources we didn't have. Particularly important to me was that patients were coming from all over the United States to the Ophthalmology Branch, which provided a unique opportunity to study hereditary retinal diseases. Furthermore, the protocol for evaluating patients in the NEI clinic served me well when I joined the Massachusetts Eye and Ear Infirmary because I observed first hand the importance of having a clinic for patients with chronic retinal degenerative diseases even though no treatments were known at that time. Furthermore, I modeled our testing protocols after those that we used in the Ophthalmology Branch.

Dr. Kupfer: Right. I was just going to ask you a question it slipped my mind. I'm sure it will come back. How did you go about the first application for research grant support?

Dr. Berson: I had an opportunity to stay as an associate ophthalmologist in the Ophthalmology Branch but I had the sense at that time that the NINDB would be reorganized and I wasn't certain that the next Director might feel the same enthusiasm for hereditary retinal disease that I had enjoyed. Around that time, Professor George Wald at Harvard College was a co-recipient of the Nobel Prize in Physiology and Medicine for his research on the retina. In 1967, the prize was awarded to Professors Wald, Hartline, and Granit. Professor Wald was working on the different color mechanisms in the eye and also was studying vitamin A metabolism, which was interesting to me, and he had assembled, as one might expect, a talented group of graduate students at Harvard College who were working on retinal function. Several scientists were working on the early receptor potential or ERP, which is the earliest component in the ERG. Therefore, although I greatly valued working at the NIH, I decided that I had to move to another institution to further my research. Dr. von Sallmann independently concluded that Professor Wald's program at Harvard College would enhance my education and he introduced me to Professor Wald and participated in arranging for me to join the Harvard faculty in August 1968.

Dr. Kupfer: When you say Harvard Department of Ophthalmology that was in Cambridge, not the Mass Eye and Ear?

Dr. Berson: Well, as you know, the Massachusetts Eye and Ear Infirmary at that time was only a five-story brick structure and was very crowded. The Howe Laboratory of Ophthalmology, which housed the Harvard research ophthalmology faculty, had very limited space. The Chairman of the Harvard Ophthalmology Department at the time, Dr. David Cogan, suggested that I could work with scientists in Cambridge and also help the Department by establishing an ERG Service at Children's Hospital in Boston, which had need for this type of testing facility. Therefore, I decided that at least on a short-term basis, I would set up the ERG Service at Children's Hospital. One of the first people I tested was Professor Wald, who graciously allowed me to evaluate his retinal function, and over the course of an entire day, we also discussed the current status of visual function testing and some possible directions for future research on retinal degenerations. I suspect he realized that I was quite serious about learning more about these electrical responses from the retina, and he therefore in turn introduced me to his fellows. One of them worked with me on the early receptor potential (ERP) 80% of my time in the first year and a half I was in Boston. We not only recorded normal ERP responses from each other but also responses from patients with various hereditary retinal diseases. We found that the ERP was abnormal in the early stages of retinitis pigmentosa.

Dr. Kupfer: Who was the fellow you worked with?

Dr. Berson: I worked with Dr. Bruce Goldstein. One of our contributions was the observation that the ERP was generated primarily by cones, whereas the slower ERG was generated primarily by rods. This sounds like a simple fact, but it took us one year to prove that the ERP was a cone-dominated response. We then studied rates of regeneration of the ERP after a bleaching flash and found that rates of regeneration of the ERP were curiously faster-than-normal in early dominantly inherited retinitis pigmentosa.

Dr. Kupfer: And who was supporting this research?

Dr. Berson: My initial support came from an NEI Center Grant to the Howe Laboratory of the Massachusetts Eye and Ear Infirmary; it was, in essence, a program project grant in which there was a position for a pediatric research ophthalmologist, which Dr. Cogan kindly assigned to me. Professor Wald also helped support this research and carefully reviewed our manuscripts before we submitted them for publication.

Dr. Kupfer: So the center grant was to the Howe Laboratory.

Dr. Berson: That was my understanding.

Dr. Kupfer: Oh, I see.

Dr. Berson: Further to your earlier question about obtaining grant support, I realized very quickly that with the establishment of the National Eye Institute that the fundamental mechanism for funding would be the individual project grant and that if I wanted to pursue an academic career, I had to compete for my own grant. To succeed in this endeavor, it was necessary to have some evidence of previous research accomplishments. The research that I did in the Ophthalmology Branch led to seven publications in peer-reviewed journals and they came out about a year after I left the NIH so when I first applied for an RO1 grant to the NEI, I had a short bibliography in the area of retinal degenerations that was very helpful in gaining support. This research in the Branch and then in Boston also provided a basis for the aims of my grant. In addition, I had volunteered to evaluate the ocular status of animals on various diets being housed in the School of Nutrition of the Harvard School of Public Health, which was located within 5 minutes of Children's Hospital; one of the animal models had ERG responses with delayed implicit times that were similar to those that we had recorded in humans with some hereditary retinal diseases. This provided a further scientific basis for my grant application to the National Eye Institute, in which we proposed to explore not only ERG responses in patients with disease but also the responses and biochemical abnormalities in this animal model. We subsequently found that the animals we were studying did not have a hereditary retinal disease but in fact had dietary taurine deficiency that could be simulated in the laboratory by placing animals on a taurine-free diet. This discovery was clinically relevant as taurine is present in breast milk but was not then present in infant formulas. It was subsequently shown by others that some patients on specialized diets without taurine supplementation for many months developed ERG changes. Today infant formula contains taurine due in part to our discovery that taurine was important for normal retinal function. We subsequently studied the plasma amino acids in patients with hereditary retinal diseases but could not find taurine deficiency. Although this line of investigation did not lead to any clinical applications for hereditary retinal diseases, this experience alerted me as to the importance of nutrition in maintaining normal retinal function; in the longer term this line of investigation has proved fruitful as we have subsequently established with NEI support that vitamin A in the palmitate form (15,000 IU/day) slows the course of retinitis pigmentosa, while high dose vitamin E supplementation appears to aggravate this condition. The Massachusetts Eye and Ear Infirmary decided that they wanted to make ERG testing a priority and therefore, the Chief of Ophthalmology, Dr. Henry Allen, moved me from the Children's Hospital to the Infirmary in January 1970 where my research career could develop further.

I would not have been able to pursue this career if I had not had extensive training in ERG recording in the Ophthalmology Branch under the direction of Dr. Ludwig von Sallmann and with the supervision of Dr. Peter Gouras. In the mid-1960's, the Ganzfeld system for ERG testing was introduced in the Branch. With this system the light stimulus is placed on top of a dome and presented to the patient as a relatively homogeneous full-field stimulus and under these conditions responses become remarkably reproducible to successive flashes of light, even with slight changes in the head or eye position of the patient being tested. This made ERG recording possible even in children. It was quite apparent that the course of retinal degeneration could be followed objectively and with great precision with this test system. The Ganzfeld ERG system has now been adopted in most clinics around the world.

Dr. Kupfer: Did Dr. Ralph Gunkel participate?

Dr. Berson: Yes, Dr. Gunkel did participate and, in fact, built a Ganzfeld system for me. He was also very helpful in teaching me the role of dark adaptation testing and other psychophysical tests in the assessment of patients with hereditary retinal disease.

Dr. Kupfer: But did Dr. Gunkel develop the Ganzfeld?

Dr. Berson: Actually, Dr. Gouras was conceptually responsible for introducing the Ganzfeld system for ERG testing. Some of the pioneering clinical work was done by Drs. Gouras, Gunkel, and Goodman.

Dr. Kupfer: Was Dr. George Goodman there with you?

Dr. Berson: Dr. George Goodman was ahead of me; he returned to New York University. Another prominent ophthalmologist who trained ahead of me in the Ophthalmology Branch was Dr. Ronald Carr, who also returned to New York University and developed a clinic for patients with hereditary retinal degenerations. The only other eye department in the 1960's placing major emphasis on hereditary retinal disease was the University of Chicago where clinical research proceeded under Dr. Alex Krill.

Dr. Kupfer: Right.

Dr. Berson: The number of clinician investigators in the area of retinal degenerations was very small in the 1960's. In retrospect, the NIH was leading the way during that period and my experience there was a very critical part of my training.

Dr. Kupfer: Good story - and it's still going on.

Dr. Berson: Dr. Kupfer, I would like to add something else to this historical record. Based on my experience, I believe in disease-oriented research. Stated in another way, one selects a human disease or group of diseases that needs study, one uses any technology that is necessary to increase the understanding of these diseases and studies animal models with these conditions, one assembles as large a group of patients as possible with the condition under study, and then one pursues rational lines of investigation in affected patients. In my case, I sought further education in molecular genetics techniques in the mid-1980's and I am sure there are other technologies that will be needed in the future. Mission-oriented or disease-oriented research is, to my mind, the best way to encourage more physicians to pursue research. Basic research for its own sake is also important as often the discoveries of basic scientists play a critical role in our capacity to do clinical research, but there must be physicians who have genuine scientific partnerships with basic researchers if we are to translate laboratory research into clinical applications. The Ophthalmology Branch at NIH provided me with the clinical and laboratory environment to begin my research on retinitis pigmentosa.

Dr. Kupfer: That's a very good point. I think that we'll stop at this time.

Dr. Berson: Thank you for asking me to provide my recollection of the Ophthalmology Branch of NIH.

Dr. Kupfer: Thank you very much.

End of transcript